

## **The Effect of Gender and Bitter Taste Phenotype on NRT Adherence and Preference**

Kate Karabinos, SN and Karen Ahijevych, PhD, RN, FAAN  
The Ohio State University

**Abstract** – As the leading cause of preventable death in the United States, cigarette smoking is a behavior that 70% of users wish they could quit (CDC, 2009). An intervention to increase cessation is nicotine replacement therapy (NRT), but adherence is variable. One reason for this could be related to an individual's bitter taste phenotype (BTP), where tasters may have an aversion to bitter flavor. Nicotine is bitter. This secondary analysis used the framework of the DHHS current evidenced-based tobacco treatment guidelines to address low smoking cessation success in women using oral NRTs. Methods: A 2 week crossover experimental design examined the relationship of BTP and gender on NRT adherence. Participants were randomly assigned to order of nicotine lozenge (continuous exposure) and inhaler (intermittent exposure). Sample: Adult smokers in the Columbus area (n=91). Conclusion: A descriptive analysis concluded that 65.5% of males and 75% of females were tasters, which is a non-significant difference according to chi square analysis. Nonparametric Mann-Whitney and Kruskal-Wallis tests showed that women had non-significantly higher adherences to both the inhaler and lozenge compared to men. Descriptive statistics were used to compute liking/satisfaction/sensory score averages. Females had significantly lower liking/satisfaction scores than men when using the lozenge on day 4. The only significant difference between genders' sensory strength scores was in the throat; female inhaler users had higher sensory score averages than male inhaler users on days 5, 6 and 7. Clinical implication: Results of this analysis conclude that women have higher sensory experiences in certain areas than men, especially in the throat and mouth, when using oral NRTs; sensory scores were inversely related to liking/satisfaction, since women had the lowest liking/satisfaction scores when sensations were high. Therefore, an intervention that decreases these sensations while pacifying the nicotine craving might be more beneficial. This analysis shows that individualized plans for smoking cessation are necessary to improve abstinence rates.

There are approximately 45.3 million people who smoke cigarettes in the United States, 70 percent of whom want to quit completely (Center for Disease Control and Prevention (CDC), 2009). Of the 70 percent who wish to quit smoking, only 44 percent have attempted to quit for more than one day. Unfortunately, the annual adult quit rate is only 2.5 percent, a statistic that has not significantly increased in years. Damaging almost every organ in the body, cigarette smoking is the leading preventable cause of death in the United States. About 90% of all deaths from chronic obstructive lung diseases are caused by cigarette smoking. Smokers double their risk of stroke, are two to four times more likely to develop coronary artery disease and are ten times more likely to develop peripheral vascular disease than nonsmokers.

There are evidenced-based smoking cessation intervention guidelines to help smokers control their cravings and ultimately quit smoking (Fiore, Ján, Baker, et. al., 2008). One such intervention is nicotine replacement therapy (NRT), which administers nicotine to the body by means other than tobacco. NRTs can be transdermal (when using the nicotine patch), or oral with the use gums, lozenges or inhalers. Adherence to NRT products is variable. One reason for such variation could be related to an individual's bitter taste phenotype, a genetic expression of taste associated with a lower tolerance for bitter flavors. Nicotine has been classified as having a bitter taste, which may explain why some individuals adhere to NRT more than others. In America, 70 percent of the population can taste the bitterness of 6-n-propylthiouracil (PROP), a phenotypic indicator for individuals who are sensitive to bitter taste (Bartoshuck, 1993). The bitterness of nicotine helps explain the significantly smaller proportion of bitter tasters in the smoking sample in a study by Enoch, Harris, Goldman, 2001. In their sample of 242 Plain American Indians, 75% of nonsmokers were bitter tasters while 50% of smokers could taste bitter.

A subset of tasters identified as supertasters have a *strong* detection of bitterness with PROP. According to previous studies, women show the *supertaster phenotype* more often than men (Enoch, 2001), which may explain why 24.8 million of the 45.3 million smokers are male (National Health Interview Survey (NHIS), 2008). Based on the information that more smokers are men, and most supertasters are women, the non-bitterness taster status of men could indicate their higher prevalence in the smoking population.

The sensory experience of smoking may also influence a smokers' ability to quit. Sensory experiences from cigarettes have been measured in locations such as the tongue, nose, back of the mouth and throat, windpipe, and chest. The sensory experience associated with different NRT products may hinder or enhance adherence to the product, depending on which sensory withdrawal symptoms are not being addressed. Smokers' gender or taster phenotype may also be correlated with sensory experience. There are immediate and long term benefits to quitting smoking, which is why it is so important to individualize smokers' treatments in order to increase the chances of smoking abstinence (CDC, 2009).

The goal of this secondary analysis was to observe the differences in the sensory experiences of women compared to men using two types of oral NRT during smoking cessation; this difference might be explained by the increased number of women supertasters. The percentage of women supertasters in the study sample will also provide information on prevalence of women who perceive bitterness as a strong intensity, which could be the cause of the low success rate with oral nicotine replacement therapies. Smoking causes an estimated \$193 billion in annual medical-related financial loss in the United States, but the most important losses are the years of human life. Smoking accounts for an estimated 438,000 deaths each year (CDC). By addressing gender differences in taster phenotype and sensory experience, smoking cessation

plans can be tailored to each individual, increasing chances of adherence and success rates. For example, a woman supertaster might have a more pleasant experience with a nicotine inhaler rather than a lozenge because of the intermittent exposure to nicotine with the inhaler, rather than continuous exposure to nicotine with the lozenge. This knowledge would allow her cessation plan to focus on interventions that address sensory and emotional needs. Because smoking is a risk factor for numerous health problems, increasing cessation rates would greatly improve public health.

## REVIEW OF LITERATURE

### *Gender*

Results from Bohadana et al. (2003) compare to those found by the CDC (2002) in that women have lower smoking abstinence rates regardless of treatment. Data from a large community intervention trial also suggests that women have lower rates of quitting than men (Bjornson et al., 1995). There is a significant correlation between the density of taste buds and fungiform papillae on the anterior tongue and perceived bitterness of PROP; supertasters have the highest density (Bartoshuck, Duffy & Miller, 1994). Previous research has shown that the proportion of super tasters is higher in women than men (Enoch, 2001), more women being supertasters and therefore having a higher density of taste receptors. Because women are less successful than men when trying to quit smoking (Perkins, Jacobs, Sanders, et. al., 2002), it is important to compare gender differences in sensory response in order to develop a treatment plan that addresses smokers' individual needs.

Women often report that smoking is helpful in reducing negative mood, enhancing positive mood, managing the stress of daily life and also managing appetite and weight gain (Mazure, McKee, O'Malley, Salovey, Krishnan-Sarin, 2005). According to Mazure, women look

to cigarettes to help them with stressful situations, making it more difficult for women than for men to give up their cigarettes. Depression and negative moods are more common among women than men, since women are more vulnerable to the negative effects of stress and are more likely to relapse back to smoking in the face of stressors than men (Mazure et. al. 2005).

### *Bitter Taste Phenotype*

Individuals vary in their taste perceptions because of their different genetic combinations. About 70% of the general population perceives the thiourea phenylthiocarbamide (PTC) as bitter in varying degrees, and the remaining 30% identify it as tasteless (Bartoshuck, 1993). The idea that individuals could perceive bitterness differently was accidentally discovered by a chemist named Arthur Fox when he was mixing powdered PTC. A few PTC particles were released into the air, and Fox's colleague vocalized how bitter the air tasted while Fox, who was much closer to the chemical, could taste nothing. It was later discovered that the ability to taste bitterness from PTC is due to an autosomally dominant allele that codes for the bitter taste phenotype. PROP and PTC are members of a class called thioureas, which share a specific chemical structure that causes the chemicals' bitter taste (Zhao, Kirkmeyer & Tepper, 2003). Those who display the phenotype are known as tasters, who often show dislike for bitter-tasting foods like broccoli, beer, caffeine, and saccharin. Nicotine has also been classified as bitter, and is the reason that there were significantly more PTC nontasters to tasters in smokers than in nonsmokers in a sample of 242 Plain American Indians (Enoch, Harris, Goldman, 2001). Some tasters perceive bitterness more intensely than others, yielding a subset of tasters known as supertasters. Supertasters also perceive more of an irritation from alcohol and capsaicin, a metabolite of chili peppers (Bartoshuck, Duffy & Miller, 1994). Bitter taste phenotype could be a

risk factor for non-adherence to oral NRT interventions due to the bitterness of nicotine. There is little information in present literature about taster phenotypes in smokers.

### *NRT and Adherence*

NRT helps provide relief from the cravings associated with smoking cessation. Oral NRT allows the individual to self-administer nicotine through an inhaler, lozenge or gum rather than a cigarette and the harmful effects of cigarette smoke. Oral NRT can significantly improve smoking cessation (Fiore, Ján, Baker, et. al., 2008) although there are varying degrees of adherence among individuals. Because nicotine is widely perceived as bitter, the bitter taste phenotype (BTP) could explain some of this variation. The use of flavors is a common technique to help dilute the bitter taste that accompanies NRT. Flavors have not increased patient adherence, but are also not authorized to fully mask nicotine's bitterness related to abuse liability concerns. NRT products help women less than they do men, while non-nicotine medications are equally effective (Perkins, Jacobs, Sanders, et. al., 2002). This difference in effectiveness might be explained by most of the supertaster population being women who would find nicotine unpleasantly bitter. The inhaler and lozenge were selected as oral NRT interventions for the primary study (from which this secondary analysis was based) because of their similar efficacies; the inhaler uses an intermittent exposure to nicotine with each inhalation, compared to the continuous exposure of the lozenge over 20 minutes. Bitter tasters may prefer the sporadic exposure to nicotine that the inhaler provides as opposed to the lozenge, which bitter tasters may find overwhelming. In a previous study in which women were randomly assigned to one of four NRT's, women adhered less than men to gum and nasal spray, but had higher adherence than men when using the inhaler (West et al. 2001), supporting the hypothesis that supertasting women may respond better to intermittent exposures to nicotine rather than a continuous lozenge

dosage, however, bitter taste phenotype was not collected in the West study. In another study, the sample preferred the inhaler in categories such as “relieves urges/withdrawal” (Schneider, Cortner, Justice, et al., 2008). The Schneider and colleagues study did not analyze the differences of preference based on gender, but did show evidence for varying preference in nicotine replacement therapies that might be explained by individual taster status. There is little information in present literature on how a smoker’s taster phenotype relates to satisfaction with oral nicotine replacement therapies.

### *Sensory Pathways*

Although research supports that nicotine plays a large role in cigarette addiction, NRT used to facilitate smoking cessation has not yielded high success rates. This could be because these interventions only address nicotine addiction, and not the sensory experience that accompanies smoking.

Replacements for the sensory effects of smoking as well as diminishing smoking-related cues may be effective in increasing smoking cessation rates. Potential approaches for devaluing smoke cues include denicotinized cigarettes, which help to condition a dislike for the behavioral aspects of smoking when not paired with nicotine. Another approach is the use of other pharmaceutical therapies (such as Chantix) a few weeks prior to an established quit day. Incorporating these approaches into a treatment program may significantly increase smoking abstinence rates (Rose, 2006).

According to Benowitz and Hatsukami (1998), men and women do not physiologically or cognitively differ with the effects of nicotine, but they do have significantly different responses to nicotine. Perkins concluded that women are less sensitive than men to pharmacodynamic effects of nicotine, suggesting that women are less sensitive to manipulations in nicotine dosage

exposure and would benefit less than men from NRT. They would be at no disadvantage for non-NRT medications.

Compared to men, smoking in women is driven mostly by non-nicotine factors rather than nicotine addiction (Perkins, Jacobs, Sanders, et. al., 2002). Non-nicotine factors include smoking-related visual, olfactory or situational cues, verbal information about cigarette nicotine content and management of smoking pattern. Verbal information about the drug content of a substance can elicit expectancies for drug effect according to studies by Perkins et al. (2006). In the study, there was no effect of nicotine dose on smoking reward and reinforcement when women were not told the nicotine content (blind conditions). When women were told accurate dose information, their reward and reinforcement measures were significantly affected; women who were told they had higher dosages of nicotine experienced significantly increased reward and reinforcement. If women are less sensitive to nicotine dose manipulations, their response to different doses of nicotine in cigarettes in the Perkin's study was due to accurate dose information. Men showed no dose effects under either instructional condition (2006).

Women used less self-administration of nicotine and placebo spray when trying to quit smoking (Perkins et al. 1996; West et al. 2001), and experienced less rewarding and reinforcing effects of nicotine dosages in both nasal sprays and cigarettes (Perkins et al. 2002). A reward is a pleasurable characteristic of the drug, according to the user. These findings indicate that women may initially become addicted to cigarettes not because of nicotine, but because they obtain a greater reinforcement from non-nicotine influences. Women show a greater decrease in smoking reinforcement when non-nicotine smoking stimuli are removed (Perkins et al., 1994; 2001). For example, when olfactory and/or visual stimuli were blocked, the smoking reward was reduced in women but not men (Perkins, Gerlach, et. al., 2001). This secondary analysis attempts to explain



preferences in oral NRT in men and women based on sensory responses to nicotine and NRT adherence. The principal questions addressed in this secondary analysis are as follows:

- Research Question 1: What is the distribution of bitter tasters among women in the sample?
- Research Question 2: Because most of the bitter tasters are women, will women have a lower adherence using an oral NRT intervention to quit smoking than men?
- Research Question 3: Will there be different sensory responses between genders when using a nicotine inhaler (which is delivered by intermittent nicotine replacement) compared to a lozenge (which administers nicotine continuously)?

## METHOD

### *Design*

A crossover experimental design (Figure 1) was implemented to address the effect of BTP, as determined by 6-n-propylthiouracil (PROP) taste methodology, on individual's use of NRT products. Participants were randomly assigned to an order of oral NRT product with 50% of participants experiencing one week of nicotine lozenge followed by one week nicotine inhaler and the other 50% of participants experiencing the reverse. Data was collected at baseline and at the end of each week for a total of 3 data collection points per participant.

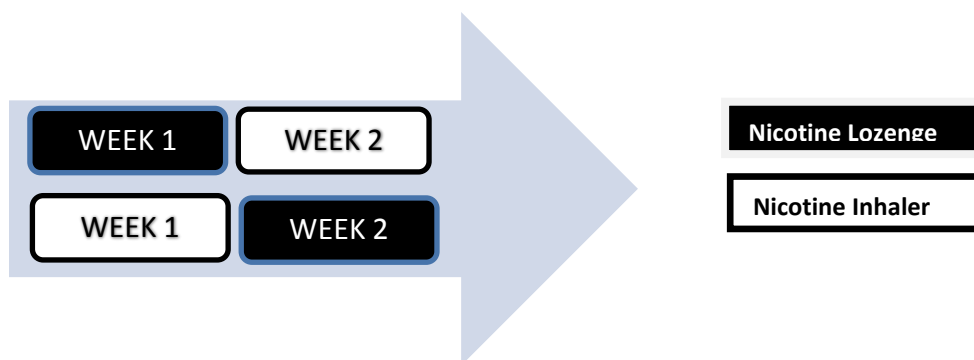


Figure 1: Crossover Design

Data on BTP and preference for certain NRT products have not been evaluated previously. Such information could be used to enhance adherence to NRT among bitter tasters. The inhaler and lozenge were selected for this study since these two products are both absorbed by oral mucosa and require similar effort for dosing and have similar efficacy of  $OR = 2.5$  for the inhaler and  $OR = 2.76$  for the lozenge (Fiore et al., 2008). The nicotine inhaler requires activity of cheeks during inhalation for at least five minutes. The two oral NRT products represent differences in time exposure potentially yielding more definitive information than would be obtained from testing only one oral NRT product. The lozenge is absorbed with continuous exposure over 20 minutes while the inhaler involves intermittent exposure with each inhalation. Bitter tasters may prefer intermittent to continuous exposure. Therefore, these two oral NRT products were deemed the best choices for addressing the research questions in this study. Unflavored products were used to simplify interpretation of the data as individual preference on flavorings would introduce more variability and require a larger sample size. Also, adding flavors to oral NRT products has little impact on palatability (Houtsmuller et al., 2002).

#### *Sample Size Justification*

Sample sizes for the experiment in the primary study were determined using information from past studies of nicotine inhaler cartridge and lozenge usage and scores on the sensory scale. Studies of nicotine inhaler use typically showed an average usage of 4.5 cartridges per day with a standard deviation around 2.1 cartridges per day (Bolliger, Zellweger, et. al., 2000). For nicotine lozenges, past studies found an average usage of 7.7 lozenges per day with a standard deviation of 3.2 lozenges per day (Muramoto, Ranger Moore, Leischow, 2003). All sample size calculations were made based on examining the effect of BTP on individual's use of oral NRT products. If we assume a correlation of 0.7 between lozenge and inhaler usage by participants,

we will need 54 individuals in each group to detect phenotype differences of a medium effect size at an alpha level of 0.05 and a power of 80%. This calculation assumes a one-sided test that bitter tasters will have lower NRT average usage than non-bitter tasters. Additional participants per group will be enrolled to cover an expected 15% attrition to yield 62 participants per group and a final sample of 124. Attrition includes individuals who do not complete follow up visits.

For the secondary study, a minimum of 45 participants is needed per group (90 total participants) to detect between a moderate and large effect of gender on sensory responses or oral NRT compliance. This sample size was based on an alpha level of 0.05 and a power of 80% for the t-test and one way ANOVA. For the chi square with an alpha level of 0.05, power of 80%, and a moderate effect size, a minimum of 87 participants are needed, so a total sample size of 90 was used (n=91) to cover all analysis requirements (Cohen, 1992).

#### *Inclusion Criteria*

Inclusion criteria was 18 through 55 years of age, smoking cigarettes for at least one year with a minimum of 10 cigarettes per day, willing to quit cigarette smoking for two weeks, not pregnant or lactating, no oral or nasal disease, no prescribed medications that may alter taste, no significant chronic or acute medical or psychiatric illnesses, no current drug abuse diagnosis, no attempts to stop smoking while using NRT in the past 3 months, no contraindications to either of the two NRT products, and no other household members enrolled in the study.

To reduce extraneous variables that potentially impact BTP, inclusion criteria included restriction to less than 56 years of age to reduce age-related changes in taste. There are a number of medications that have altered taste perception in laboratory experiments with humans including antihypertensives in which bitter perception was reduced (labetalol) or increased (diltiazem and hydrochlorothiazide) (Zervakis, Graham & Schiffman, 2000). Three

antiarrhythmic medications tested led to a reduction in bitter perception ranging from 23.9% to 49.4%. Taste detection of four tricyclic antidepressant medications was evaluated in a laboratory setting and each had a predominantly bitter taste with other qualities including metallic, sour and sharp-pungent (Schiffman, Zervakis, Suggs, Cole-Budd, Luga, 2000). In addition, these medications exhibited differential suppression of other tastes with a decreased perception of bitter. Amitriptyline HCl, another tricyclic antidepressant, was found to have a bitter, unpleasant taste of its own and blocked responses to other taste stimuli when applied continuously to the tongue (Schiffman, Zervakis, Suggs, Shaio, Suttely, 1999). Therefore, persons taking prescribed medications other than oral contraceptives were excluded. Lastly, being pregnant or lactating are contraindications for use of NRT.

### *Recruitment*

Recruitment of participants in the primary study was implemented through several mechanisms. We have been successful in recruiting for previous studies with advertisements placed in free neighborhood weekly newspapers distributed to residences. These can be targeted to any of 30+ specific neighborhoods in the Columbus metropolitan area to increase socioeconomic and ethnic diversity. Flyers were placed in campus buildings as well. Participants responded to advertisements by phone or email. These options were used successfully in previous studies. Beginning in September of 2010, the low proportion of nontasters enrolled resulted in a modification of our enrollment plan. We initiated a 2-step process with bitter taste phenotype screening as step 1 such that only nontasters are now enrolled to reach our target nontaster enrollment of 62. This is a modification of our initial recruitment plan where all individuals meeting inclusion and exclusion criteria were enrolled.

### *Procedure*

A staff member telephoned each interested person to determine eligibility (inclusion & exclusion criteria), or provided an electronic Zoomerang survey with the same questions. At the baseline face-to-face visit, a history and physical examination focused on contraindications to NRT was completed by a nurse practitioner who was a co-investigator on the study. Written IRB consent was obtained by the project nurse. Project staff described the protocol and explained the random assignment to order of oral nicotine replacement product. HIPAA guidelines were followed throughout.

Participants were seen face-to-face at baseline and the end of weeks 1 and 2 as outpatients in the Clinical Research Center (CRC), part of OSU's recently funded Clinical and Translational Science Award (2008-2013). The primary study is an example of translational research as potential findings may ultimately modify clinical practice. Subjects were instructed to smoke normally before the baseline visit. See Table 1 for procedures at each data collection time point. Nicotine addiction and smoking history provide additional individual characteristics. Baseline cotinine concentrations when smoking were used to calculate percentage of replacement compared to cotinine concentrations obtained after one week of each oral NRT product. Information on number of NRT lozenges and inhalers used daily, as well as daily sensory experiences elicited by the Duke Sensory Scale were recorded by the participant on forms provided. The outcome data collector, who was blinded to participants' bitter taste phenotype, received these data at face-to-face visits on Days 7 and 14.

<b>Time</b>	<b>Data Collected</b>	<b>Person Responsible</b>	<b>Location</b>
Baseline	Informed consent BTP testing Informed consent Demographic, smoking history questionnaire, cigarette sensory responses (Duke Sensory Scale) Saliva sample for cotinine assay Exhaled carbon monoxide Instructions for week 1 oral NRT Instruction regarding self-report logs	Project Nurse “ “ “ “ “ “ “ “	Outpatient CRC
Daily	NRT intake record (daily Log) Sensory responses (Duke Sensory Scale) Smoking slips (daily Log)	Participant	Home
Day 7	Collect daily self-report logs – NRT use; sensory scale; smoking slips Saliva sample for cotinine assay Exhaled carbon monoxide Assess NRT side effects \$100 incentive Instructions for week 2 oral NRT	Outcome data collector “ “ “ Project Nurse “	Outpatient CRC
Daily	As on “Daily” above	Participant	Home
Day 14	As on Day 7 (except no further instructions needed)  BTP testing; final payment of \$100	Outcome data collector  Project Nurse	Outpatient GCRC
Follow-up	Debriefing letter including BTP status will be sent to participants	Project Nurse	

**Table 1. Data collection procedures at baseline and end of weeks 1 and 2**

### *Protocol*

To ensure participants’ NRT use followed recommended frequency and duration, NRT product was provided at no cost to the participant as part of the research protocol. At baseline, the project nurse provided instructions on the randomly assigned oral NRT product and distributed a 1-week supply of the relevant NRT. Recommended dosage for nicotine lozenges are at least 9 lozenges per day at 1-2 hr intervals allowing it to dissolve slowly over 20-30 minutes. Nicotine inhaler instructions included proper insertion and activation of nicotine cartridges into the mouthpiece with 6 to 16 cartridges per day recommended. A nicotine cartridge delivers nicotine for approximately 20 minutes of active puffing and is absorbed in the mouth. Ambient

temperatures of 60° F are recommended as cold temperatures reduce the amount of nicotine inhaled. Side effects reported for nicotine inhaler include coughing (16-40% of cases) and throat and/or mouth irritation (15-50% of cases) (Schneider, Olmstead, Franzon, Lunell, 2001). These reactions were all mild and tolerable. Side effects of nicotine lozenge were hiccups (15%), nausea (12%), and dyspepsia (9%), which were tolerable and transient and incidence decreased during treatment (Glover, Glover, Franzon et. al., 2002).

### *Retention*

Attrition was addressed by the following: 1) participant's stated commitment to quit smoking for two weeks as a condition of enrollment; 2) participants were given the toll-free Ohio Tobacco QuitLine phone number. QuitLine smoking cessation counseling has an Odds Ratio of 1.6 (1.4-1.8) (Fiore, Ján, Baker, et al. 2008); 3) participants received \$100 at the end of week one, and an additional \$100 upon completion of week two; and 4) maintaining friendly but efficient face-to-face sessions demonstrated that we valued each participant's time. To further improve participant retention over the 2 week protocol, contact information (address, phone and email) was obtained for the participant and for a family member or friend who would be aware of the participant's location. Finally, weekly assessment of smoking status with exhaled CO provided feedback to the participant on nonsmoking success and verified smoking relapse.

## MEASURES

Sociodemographic and smoking history information was collected, as well as individual characteristics of BTP and nicotine addiction. In addition, differential oral sensory experiences with the two NRT products and NRT adherence were assessed.

### *Socioeconomic Information*

Information including age, employment, income and marital status was obtained. Smoking history was assessed with an instrument used previously and included the age the individual began smoking, current cigarette brand, average number of cigarettes consumed on a weekday, average number of cigarettes consumed on each weekend day, use of other tobacco products, number of previous serious quit attempts, perception of smoking prevalence among peers, percentage of friends who smoke, as well as cigarette smoke exposure in their residence and work environment (Ahijevych, Parsley, 1999). All questionnaire forms were developed in TELEform<sup>®</sup> software (Cardiff Software Inc, Crows Nest, NSW, Australia) with data scanned and verified electronically to reduce error.

### *Bitter Taste Phenotype*

BTP was determined at the baseline enrollment visit. Participants rated the intensity of the taste of a 1.5 cm diameter paper disk with 1.0 mol/l NaCl solution first, followed by the PROP filter paper disk impregnated with a 50 mmol/l PROP solution (Zhao, Kirkmeyer & Tepper, 2003). A Labeled Magnitude scale was used where three taster groups were classified as: non-tasters with intensity rating of 15 mm or less on the scale, medium tasters from 16 mm through 67 mm, and super tasters above 67 mm. When a participant marked a borderline rating on PROP, it was compared to the rating for NaCl to clarify group assignment (Tepper, Christensen, Cao, 2001). In analyses, medium and super tasters formed the taster group and were compared to the non-taster group. Significant test-retest reliability of this protocol has been reported (Zhao, Kirkmeyer & Tepper, 2003) and external validity was established comparing the two-disk methodology to a three-solution test. Degree of agreement between the two classification procedures was high (coefficient of association  $P=0.74$ ) and significant (Schneider,



Cortner, Justice et. al., 2008). Bitter taste status was determined at baseline and at the end of week 2 to characterize potential changes with short-term smoking cessation.

#### *NRT Product Sensory Evaluation*

The Duke Sensory Scale (Westman, Behm, Rose, 1995) instrument was used to obtain participants' evaluation of the nicotine inhaler and lozenge. Scores were collected at baseline regarding smoking, and daily regarding sensory experiences of each oral NRT product. An average for each condition (one week) was computed, although participants who omitted any daily score caused problematic computation of averages (as explained in the results section). Areas addressed by the instrument included strength of sensations during use in five locations, as well as liking of the product, and level of satisfaction. The 7-point ordinal scale ranges from "not at all" (1) to "extremely" (7). A sum of the 7 items could yield a possible range of 7 to 49. Test-retest reliability of the mouth/throat sensation ratings from day 1 to the end of week 1 with the same cigarette stimulus was highly correlated (Spearman's  $\rho = 0.81$ ,  $p = 0.0001$ ) (Westman, Behm, Rose, 1995).

#### *NRT Adherence*

Daily use of NRT was defined as the number/day for nicotine lozenge and inhaler cartridges recorded by the participant on daily logs specific to oral nicotine lozenge or inhaler (Muramoto, Ranger Moore, Leischow, 2003). For example, the NRT inhaler log asked participants to identify the time each day that a cartridge was initiated and the length of time it was used. Collecting log data on a daily basis reduced recall bias. The logs were brought to face-to-face visits at the end of weeks 1 and 2. Participants were provided sufficient quantities for each week long period. Participants were asked to return unused NRT product and used packaging to validate usage self-report, and were asked how they used the product. Participants' reasons for

under-using NRT, if present, were collected during the face-to-face visits. Potential responses included: forgot, not helping, side effects, did not need it, and bitter taste (West, et. al., 2001). Frequency and degree of side effects of NRT therapy, such as indigestion or mouth irritation with nicotine lozenge, and persistent mouth or throat irritation or cough with nicotine inhaler was determined by the outcome data collector at the weekly visit. For descriptive analyses only, percentage of recommended NRT dosage consumed was calculated using recommended NRT dosage in each condition as the denominator. In the primary study, a combination of cotinine concentration and carbon monoxide in exhaled air measures was used to classify NRT adherence and smoking status. For example, if an individual's cotinine was  $>20$  ng/ml and CO confirmed smoking abstinence, they would be categorized as using NRT as recommended and a nonsmoker. There were 4 outcomes regarding oral NRT adherence: NRT use and not smoking; NRT use with concurrent smoking; no NRT use and not smoking; and no NRT use and concurrent smoking. All participants were retained in analyses.

### *Analysis Methods*

The design used for this experiment was a crossover design wherein each subject was exposed to both treatments and the randomized order of treatments reverses between subjects. The research questions of the secondary analysis are answered as follows:

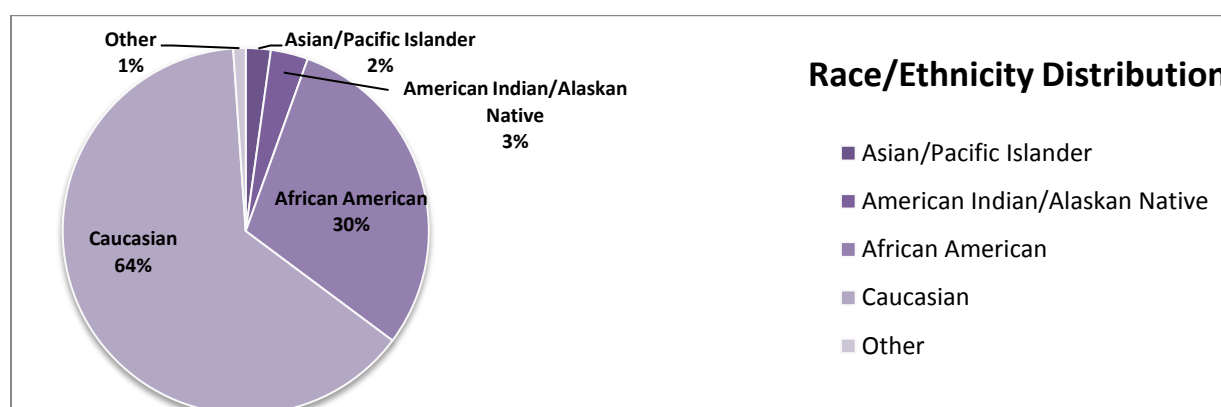
- To address research question one, which examined the distribution of tasters among men and women in the sample, a descriptive analysis and chi square were used to analyze the collected data.
- To address research question two, nonparametric Mann-Whitney and Kruskal-Wallis tests were used as an appropriate analysis tool to assess women's adherence using an oral NRT intervention to quit smoking in comparison to that of men.

- To address research question three, descriptive statistics were used to compute liking/satisfaction/sensory score averages. Nonparametric Mann-Whitney and Kruskal-Wallis tests were used to compare the liking, satisfaction and sensory scores between the two independent variables (gender and product).

## RESULTS

### *Sample Description*

The sample included 91 participants with an average age of 32.5 years ( $SD = 10.3$ ), 55 of whom were male (60%) and 36 were female (40%). Smoking patterns of the sample included an average of 14.1 years of regular smoking ( $SD = 10.3$ ) at a rate of 15.5 cigarettes per day ( $SD = 6$ ). The participants had an average of 2.1 serious attempts to quit smoking in their lifetime. When asked to rate their addiction to cigarettes from 1-100 (with 100 being maximum addiction), the average addiction rating was 76.8 ( $SD = 20.8$ ). Of the 91 participants, 63.7% of participants were Caucasian, 29.7% were African American and 3.3% were American Indian or Alaskan native (Figure 2).



**Figure 2: Race/Ethnicity Distribution of the Sample (n = 91)**

### *Distribution of Tasters*

Of the 91 participants, 69.2% were tasters. Of the males, 65.5% were tasters; 75% of females could also taste the bitterness of the PROP strip (Figure 3). Using a chi square analysis, there was no significant difference in the distribution of tasters between males and females ( $\chi^2 = 0.931$ ,  $p = 0.335$ ).

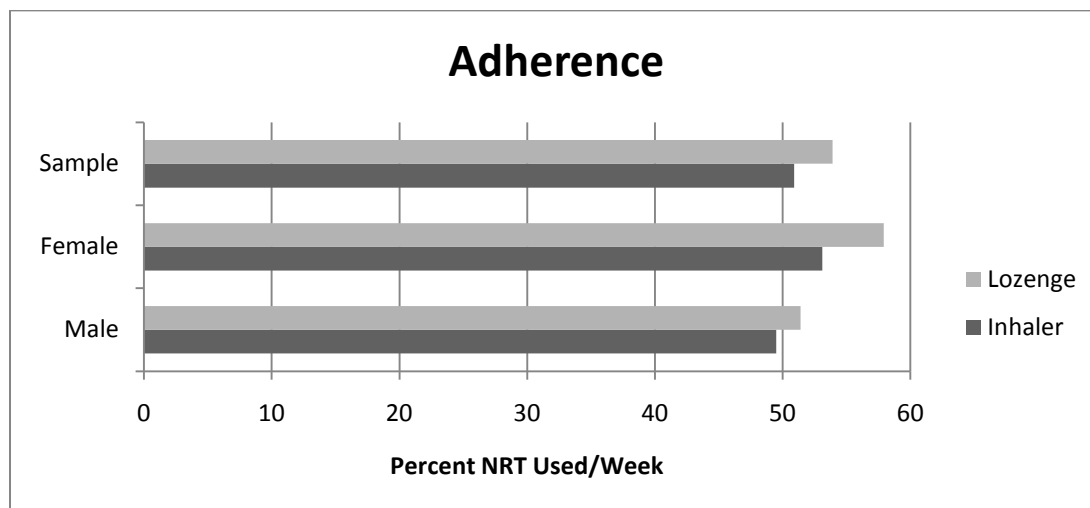


**Figure 3: Percentage of Male and Female Tasters and Nontasters (n=91)**

### *Adherence Using NRT Intervention*

NRT adherence for this study was defined as the percentage of NRT product (inhaler or lozenge) used over the assigned week for the specific NRT. This is calculated as the number of NRT used over the week divided by the recommended dosage provided at the beginning of the week. The recommended dosage for each NRT was 60 lozenges or 54 inhalers per week (Fiore et al., 2008). Men's use of the inhaler had a mean adherence of 49.5% (SD = 27.7), while men's use of the lozenge had a mean adherence of 51.4% (SD = 24.4) (Figure 4). Women had a 53.1% adherence (SD = 27.8) when using the inhaler and 57.9% (SD = 29.7) adherence when using the lozenge (Figure 4). The sample as a whole had a non-significantly higher adherence to the lozenge, with a mean adherence of 53.9% (SD = 26.6) compared to the mean adherence to the

inhaler of 50.9% (SD = 27.6) (Figure 4). Unequal gender group sizes lead to the use of nonparametric statistics; Mann-Whitney and Kruskal-Wallis tests showed no significant differences between men and women's adherence when using lozenge ( $p = 0.364$ ) or inhaler ( $p = 0.526$ ).



**Figure 4: Percentage of NRT Adherence by Gender and NRT Product (n=91)**

#### *Liking and Satisfaction of NRT*

The Duke Sensory Scale was used to assess participant liking and satisfaction of each product. The scale ranges from “not at all” (1) to “extremely strong” (7); the scores from each day were summed to compute a total sensory experience for one week (7 days) of each NRT. Adding the scores from each day to produce a weekly total was problematic since some participants omitted sensory scores for one or more days; when this occurred, the subject's scores for the other days were also excluded from the calculation of average liking or satisfaction for the week, resulting in lower participant numbers due to a single missing data point. For example, there were 70 complete data sets for satisfaction with the lozenge for the week. This means that 21 participants had at least one missing data point. Therefore, liking and satisfaction scores for each day were used to describe daily liking and satisfaction with each NRT product.

Nonparametric Mann-Whitney and Kruskal-Wallis tests were used to compare liking and satisfaction by gender because of the greater number of male participants in the sample.

Daily satisfaction score averages ranged from 2.67 to 4.30; the lowest averages were reported from females using the lozenge, especially after day 4 when the liking average dropped to 2.73 (SD = 1.6) among females. This produced a significant difference in satisfaction scores ( $p = 0.04$ ) between male and female lozenge groups on day 4, since the male lozenge group's satisfaction average was 3.49. The highest satisfaction scores were from males using the inhaler, followed by females using the inhaler (Figure 5, Table 1). The sample as a whole had higher satisfaction scores using the inhaler.

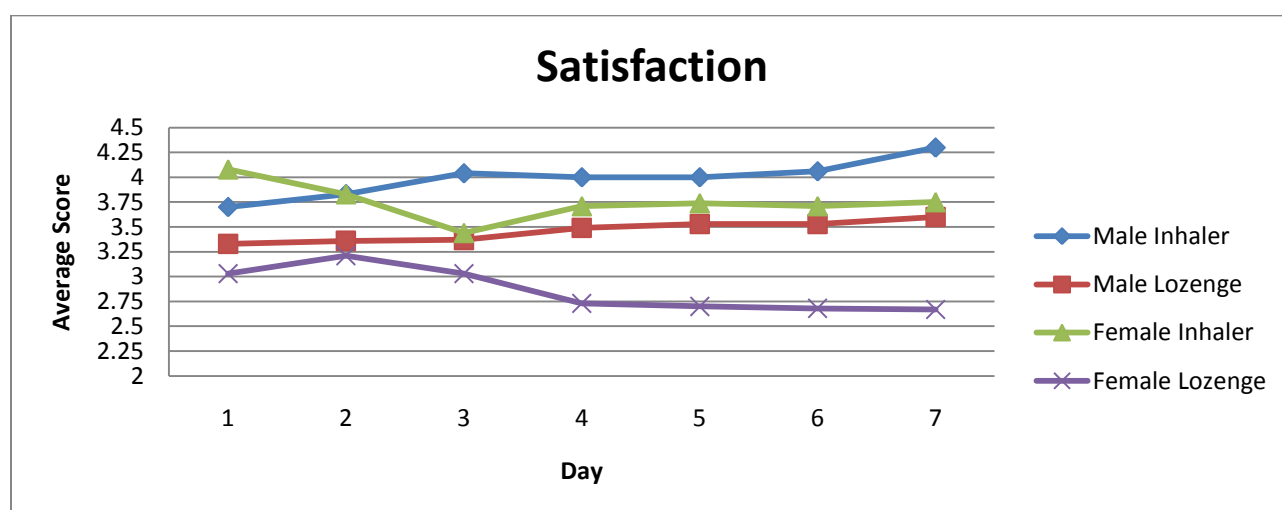


Figure 5: Daily Satisfaction with NRT Product by Gender and Inhaler and Lozenge

	Male (Inhaler)	Male (Lozenge)	Female (Inhaler)	Female (Lozenge)
Day 1	3.70 (n=54)	3.33(n=54)	4.08(n=36)	3.03(n=34)
Day 2	3.83 (n=53)	3.36(n=53)	3.83(n=35)	3.21(n=33)
Day 3	4.04 (n=51)	3.37 (n=51)	3.44 (n=34)	3.03 (n=33)
Day 4	4.00 (n=50)	3.49* (n=53)	3.71 (n=35)	2.73* (n=33)
Day 5	4.00 (n=49)	3.53 (n=53)	3.74 (n=35)	2.70 (n=33)
Day 6	4.06 (n=50)	3.53 (n=51)	3.71 (n=34)	2.68 (n=34)
Day 7	4.30 (n=50)	3.60 (n=50)	3.75 (n=32)	2.67 (n=30)

\* = Significant ( $p < 0.05$ )

Table 1: Daily Average Satisfaction Ratings for Inhaler and Lozenge by Gender

Liking score averages ranged from 2.12 to 4.16 and were similar to the satisfaction results with the sample as a whole scoring higher liking averages when using the inhaler. Also parallel with satisfaction were the higher average liking scores of males using the inhaler with an average liking of 4.16 (SD = 1.67) (Figure 6, Table 2). The group with the second highest averages was the female inhaler NRT group (Figure 6, Table 2). The lowest liking score averages were from females using the lozenge NRT, especially on and subsequent to day 4 when the average dropped from 2.56 (day 3) to 2.12 liking on day 4 (Figure 6, Table 2). This is a similar finding to that of the satisfaction score averages, as there was a significant difference ( $p = 0.047$ ) in liking averages between males (2.81) and females (2.12) using the lozenge on day 4.

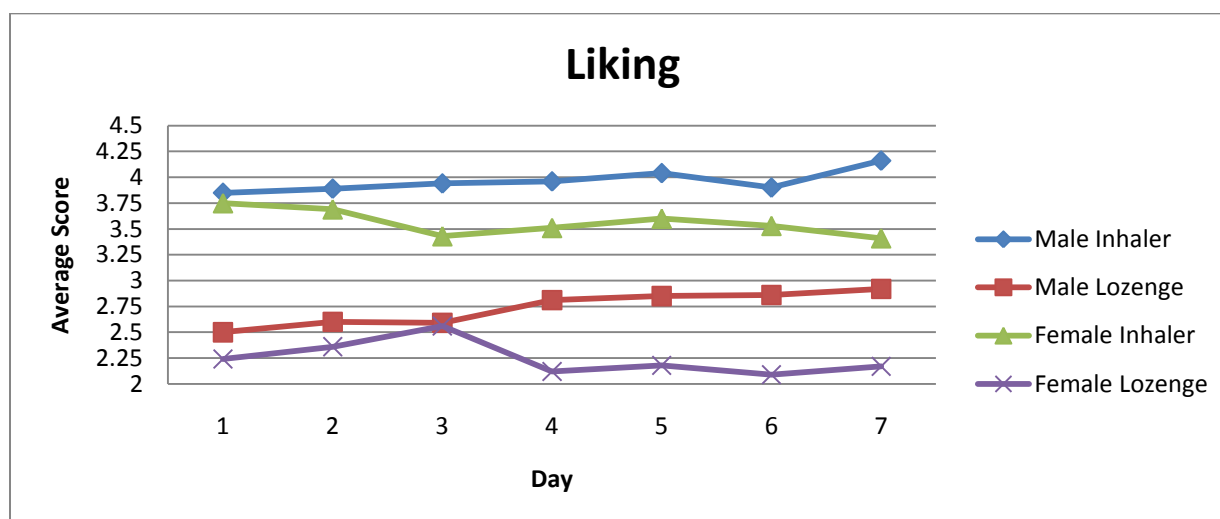


Figure 6: Liking of NRT Product by Gender and Inhaler and Lozenge

	Male (Inhaler)	Male (Lozenge)	Female (Inhaler)	Female (Lozenge)
Day 1	3.85 (n=54)	2.50 (n=54)	3.75 (n=36)	2.24 (n=34)
Day 2	3.89 (n=53)	2.60 (n=53)	3.69 (n=35)	2.36 (n=33)
Day 3	3.94 (n=51)	2.59 (n=53)	3.43 (n=35)	2.56 (n=33)
Day 4	3.96 (n=50)	2.81* (n=53)	3.51 (n=35)	2.12* (n=33)
Day 5	4.04 (n=49)	2.85 (n=53)	3.60 (n=35)	2.18 (n=33)
Day 6	3.90 (n=50)	2.86 (n=51)	3.53 (n=34)	2.09 (n=34)
Day 7	4.16 (n=50)	2.92 (n=50)	3.41 (n=32)	2.17 (n=30)

\* = Significant ( $p < 0.05$ )

Table 2: Daily Average Liking Ratings for Inhaler and Lozenge by Gender

### *Sensory Experience of NRT*

Each participant rated the strength of sensation felt on the tongue and in the nose, back of the mouth (throat), windpipe and chest from “not at all” (1) to “extremely strong” (7) using the Duke Sensory Scale. A daily sensory strength score was computed as the mean of the participant’s sensory ratings from each designated location (tongue, nose, throat, windpipe, and chest) for 7 days with each NRT. There were no significant differences between men and women’s daily sensory strength scores by NRT product. Male inhaler strength scores were the lowest averages and declined as the week progressed, ranging from 2.77 to 3.0 (Table 3, Figure 7). The highest average strength ratings were those of women using the lozenge from days 1 through 4 with scores ranging from 3.21 to 3.38; the highest average sensory score was from this group on day 4 with a score of 3.38 on a range of 1 to 7. After day 4, the highest scores were from women using the inhaler with scores ranging from 3.08-3.22 (Table 3, Figure 7). Daily versus weekly sensory scores were used for the same reason daily liking and satisfaction scores were analyzed; participants who omitted data from any day were not included in weekly average analyses.

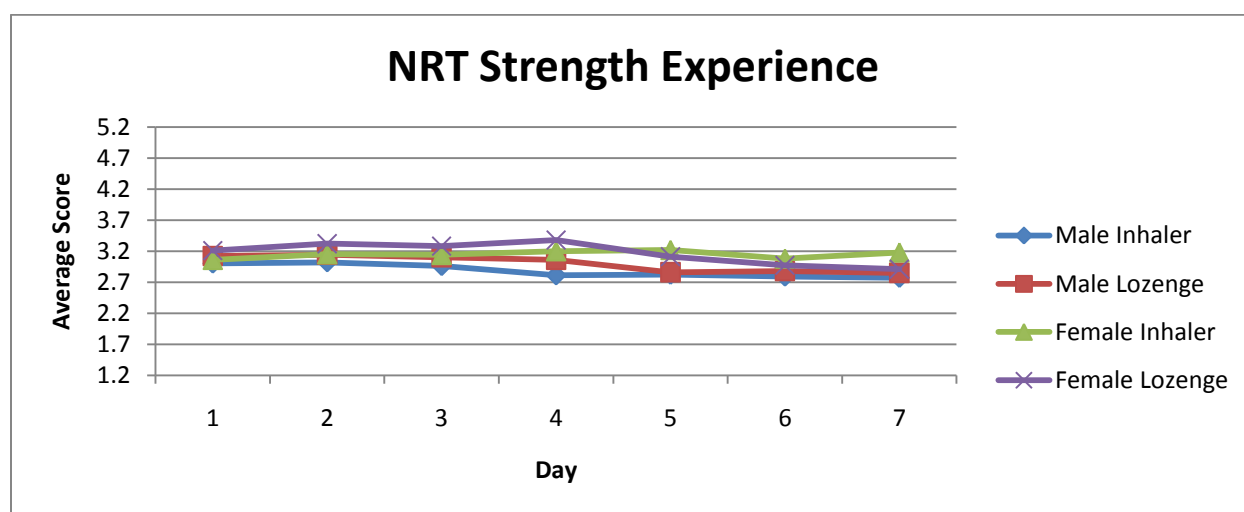


Figure 7: Strength with NRT Product by Gender and Inhaler and Lozenge



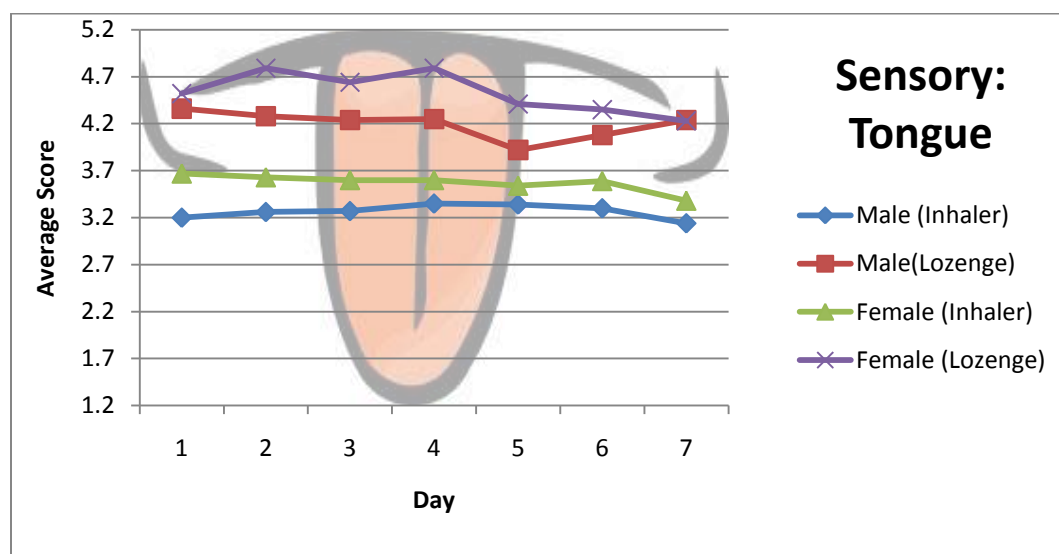
	MALE (Inhaler)	MALE (Lozenge)	FEMALE (Inhaler)	Female (Lozenge)
<b>Day 1</b>	3.0 (n=54)	3.12 (n=53)	3.06 (n=35)	3.21 (n=33)
<b>Day 2</b>	3.02 (n=53)	3.14 (n=52)	3.15 (n=34)	3.32 (n=33)
<b>Day 3</b>	2.96 (n=51)	3.10 (n=51)	3.14 (n=35)	3.28 (n=32)
<b>Day 4</b>	2.81 (n=49)	3.06 (n=53)	3.20 (n=35)	3.38 (n=33)
<b>Day 5</b>	2.82 (n=49)	2.86 (n=53)	3.22 (n=35)	3.11 (n=32)
<b>Day 6</b>	2.79 (n=49)	2.88 (n=51)	3.08 (n=32)	2.97 (n=33)
<b>Day 7</b>	2.77 (n=50)	2.85 (n=50)	3.18 (n=32)	2.91 (n=30)

\* = Significant ( $p < 0.05$ )

**Table 3: Daily Average Strength Ratings for Inhaler and Lozenge by Gender**

### *Internal Sensory Sensations*

On the tongue, female lozenge users had the highest strength sensation averages with a range of 4.23 to 4.79. Lowest sensory strength averages on the tongue were reported by males using the inhaler (Figure 8.1). Each group had different sensory scores for the tongue, and the scores tended to be similar for each gender-product group.



**Figure 8.1: Strength on Tongue with NRT Product by Gender and each NRT**

In the throat, women using the lozenge had the highest sensory scores, including the maximum score of all areas on day 4 with a score average of 5.09 (SD = 1.7). After day 4, score averages for this group dropped steadily each day. Males using the inhaler had the lowest scores in the throat with a score range of 3.64 to 4.28 (Figure 8.2). The results of sensory scores in the

throat correspond with those of the tongue; the female lozenge group had the highest scores that trended downward over the week while the male inhaler group had the lowest scores in both areas.

The only significant difference between genders' sensory strength scores were in the throat (Figure 8.2). These significant differences in strength scores were found between male and female inhaler users on day 5 ( $p = 0.02$ ), day 6 ( $p = 0.03$ ) and day 7 ( $p = 0.025$ ). On Day 5, male inhaler users had an average strength score of 3.8 while females average strength score was 4.74. On day 6, males' average strength score was 3.73, significantly lower than the 4.62 female average. The greatest difference was on day 7, when the male average (3.64) was 0.89 lower than the female average (4.53).

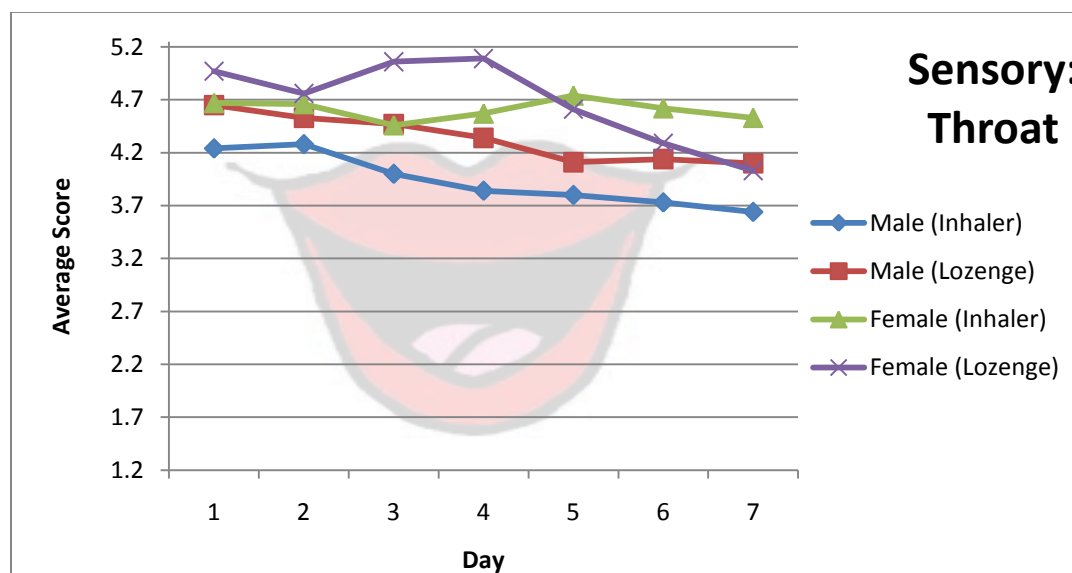


Figure 8.2: Strength in Throat with NRT Product by Gender and each NRT

The lowest strength sensory scores were reported in the nose, windpipe and chest. The minimum scores from the mouth and throat were higher than the maximum scores related to the nose, windpipe and chest. In the nose, the female inhaler group had the higher scores and the male lozenge group had the lowest (Figure 8.3).

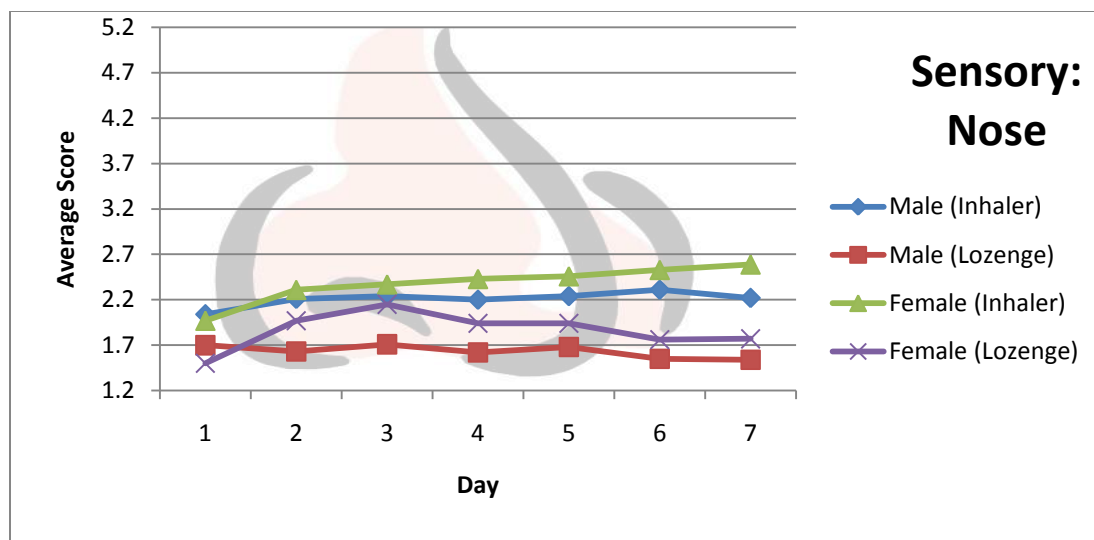


Figure 8.3: Strength in Nose with NRT Product by Gender and each NRT

Scores in the windpipe were similar in all NRT groups, but the highest score average was reported by the male inhaler group (Figure 8.4). The chest sensory score range was 1.80 to 2.46, making it one of the lower scored strength sensation areas. The female inhaler group had higher score averages especially after day 3 (Figure 8.5).

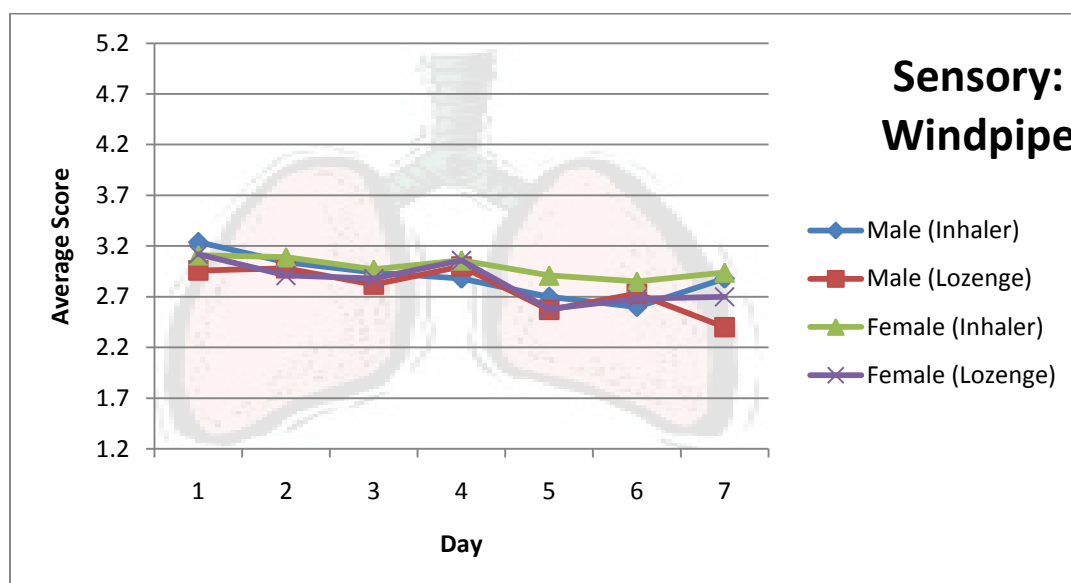


Figure 8.4: Strength in Windpipe with NRT Product by Gender and each NRT

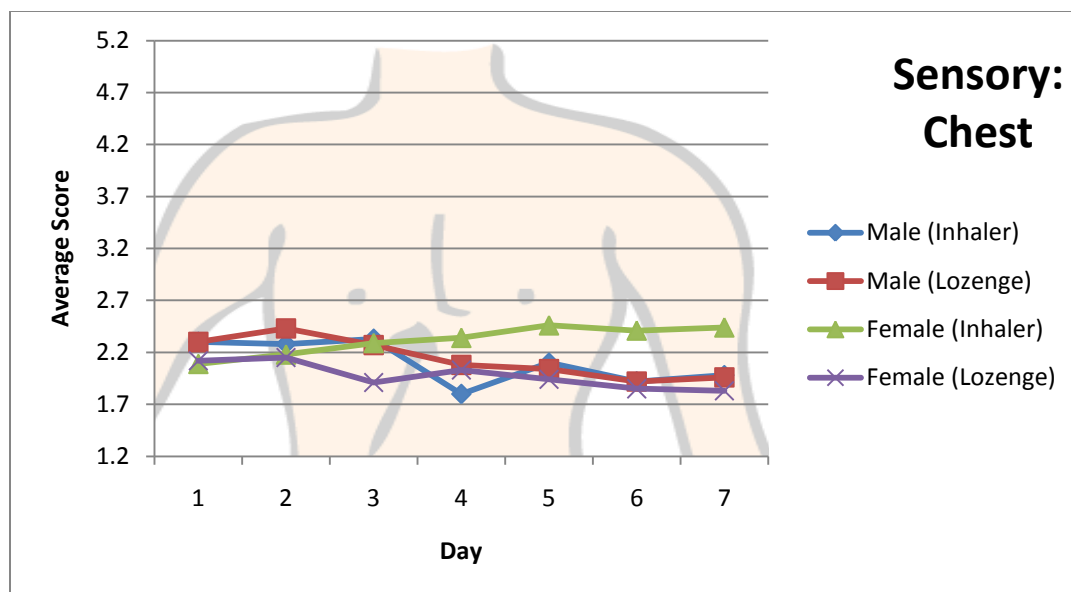


Figure 9: Strength in Chest with NRT Product by Gender and each NRT

The highest sensory scores were in the throat and mouth, especially in females using the lozenge NRT (Figures 8.1 to 8.5). The lowest scores were in the nose from the female lozenge group, which had a score average of 1.5 on day 1 (Figure 8.3). The male inhaler group had the overall lowest scores, especially in the tongue, throat and chest. Scores peaked at different times throughout days 1-7, although most sensory scores declined toward the end of the week (after day 4).

## DISCUSSION

The taster percentage of the sample (69.2%) is comparable to the 70% of PROP tasters in the United States' population (Bartoshuck, 1993). To address research question 1, 75 percent of women were tasters which is comparable to Enoch et al.'s finding that 71% of women were tasters (2001). Of the 63 tasters in the sample, 42.9% were female but it is important to consider the higher number of men in the sample. In the study by Enoch, Harris & Goldman (2001), there was a significantly higher percentage of women tasters than male tasters. In this analysis, there was a non-significantly higher percentage of female tasters compared to male tasters. In contrast,

the proportion of men who were tasters in this analysis (65.5%) was higher than the 56% found by Enoch et al. (2001).

Research question 2 inquires about women's adherence to the oral NRT interventions. Women had non-significantly higher adherence rates to both the inhaler and the lozenge (53.1% adherence and 57.9% adherence, respectively) than men (49.5% adherence and 51.4% adherence, respectively). A paired t-test was used to determine that there was not a significant difference in women's adherence to the inhaler versus the lozenge. In other studies, women had significantly higher 15 week abstinence rates than men using the inhaler ( $p=0.01$ ) (West et al. 2001). Therefore, there is a possible connection between higher adherence rates in this study and greater smoking abstinence rates in women in the West et al. (2001) study. There was no significant difference in number of serious lifetime quit attempts by gender, so motivation to adhere to the NRT intervention was not influenced by different quit histories. Only one person had ever tried using the inhaler before, and only one person had ever attempted quitting with the lozenge, so any differences in liking, satisfaction or adherence were not influenced by bias from previous use of the NRT.

Research question 3 assesses the sensory differences between genders when using different NRT's. Females using the lozenge had the lowest satisfaction score averages, especially after day 4 when the liking average dropped to produce a significant difference in satisfaction scores ( $p=0.04$ ) between male and female lozenge groups. The sample had overall higher scores using the inhaler; the highest satisfaction scores were from males using the inhaler, followed by females using the inhaler (Figure 5, Table 1). Men trended from lower to higher satisfaction scores over the week with use of both the lozenge and inhaler, while females trended downward over the seven days in each NRT category.

Liking results were similar in that the inhaler produced highest liking average scores in both genders. The highest liking averages were from male inhaler users followed by female inhaler users. Analogous to satisfaction scores, there was a significant difference ( $p=0.047$ ) in liking averages between males (2.81) and females (2.12) using the lozenge on day 4. The significant decrease in satisfaction and liking of the lozenge for females on day 4 did not affect adherence, since women had the highest adherence to the lozenge.

There were no significant differences between men and women's daily overall perceived sensory strength scores by NRT product. Male inhaler strength scores were the lowest averages and declined as the week progressed, but their satisfaction and liking averages increased. The highest average sensory score was from women lozenge users on day 4, which is congruent with the significantly lower liking scores for women lozenge users than men on day 4. The highest sensory scores were in the throat and tongue, especially in females using the lozenge NRT (Figures 8.1 to 8.5). There were significantly higher sensory score averages in the throat for females on day 5, day 6, and day 7 using the inhaler compared to men. The lowest strength sensory scores were reported in the nose, windpipe and chest. The male inhaler group had the overall lowest scores, especially in the tongue, throat and chest. Males always had the lowest sensory scores in each area. Highest sensory scores were always from a female group, except for in the windpipe.

There is limited research on gender and sensory experiences of nicotine replacement therapy. In a study by Westman et al. (1995), higher airway sensations are beneficial because they are similar to those of cigarettes. In the same way that intravenous alcohol cannot provide the same taste as an orally consumed alcoholic beverage, nicotine replacement cannot provide the airway sensations of cigarette smoke. Because the airway sensations have always been linked

to the nicotine effect, smokers may gauge their nicotine intake according to these airway sensations. If nicotine is provided without the airway sensations, smokers may not realize that they are receiving nicotine, and may begin smoking again to receive the airway sensations that they have come to associate with the nicotine effect (Westman et al., 1995). In the Westman study, a citric acid inhaler improved 10-week smoking abstinence rates over lactose inhaler because the citric acid mimicked the strong airway sensations of a cigarette. This could explain the higher adherence rates of the women, since their BTP could indicate a greater need for the airway sensations. This idea is supported by the higher liking and satisfaction of the inhaler group rather than the lozenge amongst females. However, liking and satisfaction decreased as sensation scores increased. Further research should address the liking and satisfaction of sensations in certain areas for those expressing the bitter taste phenotype.

The sensory scores in each area were inversely related with liking and satisfaction scores, since female lozenge users had the lowest liking and satisfaction scores and the highest sensation score averages. Male inhaler users had the highest liking and satisfaction scores, while in turn scoring the lowest in the sensory areas. Females tended to trend downward in their liking and satisfaction while trending upward in most of their sensation score areas.

It was difficult to determine whether strength of sensation was associated with liking or satisfaction; women had low satisfaction/liking scores with the lozenge and higher sensation scores, but had higher lozenge adherence. Adherence could be influenced by many factors such as the participant's social support system, level of addiction, and motivation to quit smoking, so the sensory score averages of the lozenge and inhaler were compared to the sensory scores of a cigarette as rated by the study participants at baseline. To avoid an unwanted transition from cigarette to oral NRT intervention, the NRT should have a similar sensory experience to that of a

cigarette. The cigarette's sensory scores in the throat, windpipe and chest had the highest averages (4.47, 4.25, and 4.21 respectively) while the nose and tongue had the lowest averages (2.99 and 2.89). The oral NRT products' sensory strength were similar in the high throat averages, but had much lower strength averages in the windpipe and chest. The NRT interventions also had much lower sensory averages in the nose and higher averages in the tongue. Higher satisfaction and liking scores were noted with use of the inhaler, which had sensory scores most similar to those of cigarettes in all sensory areas. This could mean that inhaled nicotine has a unique and enjoyable sensory experience.

The significantly lower female lozenge satisfaction and liking scores on day 4 could be explained by the unmasking of the bitter taste phenotype over time after smoking cessation exhibited by higher strength scores after day 4. Lozenges were also least similar to cigarettes in sensory strength, which may have become more evident to the participant over time.

### *Limitations*

Day 4 changes in liking, satisfaction and sensory strength may be attributed to ability to taste bitterness increasing as length without a cigarette increases—assessing taster status when men/women are still smoking might mask taster phenotype, which may become apparent over time.

This study had more men than women, as well as a very low nontaster sample which eventually required participant pre-screening. The study only took place for the duration of 2 weeks, which limited the study. An equal amount of men and women, and a greater nontaster sample over a longer duration of time would yield better results. The study also did not clarify the participants' perceived bitterness each day with each oral NRT intervention, making it difficult to associate sensory strength with bitter taste phenotype.



### *Clinical Implications*

Women used less self-administration of nicotine and placebo spray when trying to quit smoking than men (Perkins et al. 1996; West et al. 2001). Compared to men, smoking in women is driven mostly by non-nicotine factors rather than nicotine addiction (Perkins, Jacobs, Sanders, et. al., 2002). Interventions that only address nicotine addiction, such as NRTs, have not yielded high success rates. This is because these interventions neglect the sensory experience that accompanies smoking. The results of this analysis conclude that women have higher sensory experiences in certain areas than men, especially in the throat and mouth, when using oral NRTs which may have been caused by BTP. Because liking and satisfaction decreased as sensation score averages increased, these increased sensations may be a negative experience for tasters, which were more often women. Therefore, an intervention that decreases these sensations while pacifying the nicotine craving might be more beneficial. More studies should be done that address the liking and satisfaction of these sensations.

Because there was not a significant difference in the distribution of tasters between genders and no significant difference in adherence to inhaler or lozenge by gender, no conclusion can be made to predict success using an oral NRT in relation to the patient's bitter taste phenotype. Bitter taste perceptions were not assessed daily with each intervention, so it was difficult to associate strength of sensation with bitter taste. This analysis does show that individualized plans for smoking cessation are necessary to improving abstinence rates; if the patient prefers the strong sensation in the throat (similar to that of a cigarette), then an appropriate NRT, like the inhaler, should be selected. If the patient dislikes strong sensations, then the lozenge might be a better option.

Direction for future research includes rating bitterness in relation to strength sensations using oral NRT's in order to utilize a patient's bitter taste phenotype to improve his or her chances for success in smoking cessation. Studies could also allocate an individual smoking cessation intervention according to BTP; tasters could be assigned to a non-oral NRT such as a transdermal patch or pharmacologic agent (i.e. Chantix or Zyban) while nontasters are given an oral NRT. Participants would then be asked to rate their liking and satisfaction to their chosen intervention.

## REFERENCES

- Ahijevych, K., Parsley, L., (1999). Smoke constituent exposure and stage of change in Black and White women cigarette smokers. *Addictive Behaviors*, 24, 115-120.
- Cohen, J. (1992). A power primer. *Psychological Bulletin*, 112, 155-159.
- Center for Disease Control and Prevention (CDC), 2009. *Smoking and Tobacco Use*. Retrieved May 05, 2009 from <http://www.cdc.gov/tobacco/index.htm>
- Bartoshuck LM. (1993). The biological basis of food perception and acceptance. *Food Quality Preference*, 4, 21-32.
- Bartoshuck LM, Duffy VB, Miller IJ. (1994). PTC/PROP Tasting: Anatomy, psychophysics, and sex effects. *Physiology and Behavior*, 56, 1165-1171.
- Benowitz, N., & Hatsukami, D. (1998). Gender differences in the pharmacology of nicotine addiction. *Addiction Biology*, 3, 383-404
- Bohadana, A.; Nilsson, F.; Rasmussen, T.; Martinet, Y. "Gender differences in quit rates following smoking cessation with combination nicotine therapy: influence of baseline smoking behavior." *Nicotine and Tobacco Research*, v. 5 issue 1, 2003, p. 111-6.
- Bolliger, C., Zellerger, J., Danielsson, T., van Bijon, X., Robidou, A., Westin, A., Perruchoud, A., & Sawe, U. (2000). Smoking reduction with oral nicotine inhalers: Double blind, randomized clinical trial efficacy and safety. *BMJ*, 321, 329-333.
- Enoch MA, Harris CR, Goldman D. (2001). Does a reduced sensitivity to bitter taste increase the risk of becoming nicotine addicted? *Addictive Behaviors*, 26, 399-404.
- Fiore MC, J  en CR, Baker TB, et al.(2008). *Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline*. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service.
- Glover, E., Glover, P., Franzon, M., Sullivan, C., Cerullo, C., Howell, R., Keyes, G., Nilsson, F. & Hobbs, G. (2002). A comparison of a nicotine sublingual tablet and placebo for smoking cessation . *Nicotine & Tobacco Research*, 4, 441-450.
- Houtsmuller, E., Fant, R., Eissenbert, T., Henningfield, J. & Stitzer, M. (2002). Flavor improvement does not increase abuse liability of nicotine chewing gum. *Pharmacology Biochemistry & Behavior*, 72, 559-568.
- Mazure C. , McKee S., O'Malley S, Salovey P. & Krishnan-Sarin S. (2005). Perceived risks and benefits of smoking cessation: Gender-specific predictors of motivation and treatment control. *Addictive Behaviors*, 30(3):423-35.

Muramoto, M., Ranger Moore, J., Leischow, S. (2003). Efficacy of oral transmucosal nicotine lozenge for suppression of withdrawal symptoms in smoking abstinence. *Nicotine & Tobacco Research*, 5 223-230.

National Health Interview Survey (NHIS), 2008. *National Center for Health Statistics*. Retrieved December 15, 2009 from <http://www.americanheart.org/presenter.jhtml?identifier=4559>

Perkins K., Epstein L., Grobe J., Fonte C. (1994) Tobacco abstinence, smoking cues, and the reinforcing value of smoking., *Pharmacology, Biochemistry and Behavior*, 47(1), 107-12

Perkins K., Gerlach D., Vender J., Grobe J., Meeker J. et al. (2001) Sex differences in the subjective and reinforcing effects of visual and olfactory cigarette smoke stimuli, *Nicotine & Tobacco Research : Official Journal of the Society for Research On Nicotine and Tobacco*, 3(2), 141-50.

Perkins, K., Doyle, T., Ciccocioppo, M., Conklin, C., Sayette, M., & Caggiula, A. (2006). Sex differences in the influence of nicotine and dose instructions on subjective and reinforcing effects of smoking. *Psychopharmacology*, 184(2), 600-607.

Perkins, K., Grobe, J., D'Amico, D., Fonte, C., Wilson, A., & Stiller, R (1996). Low-dose nicotine nasal spray use and effects during initial smoking cessation. *Experimental and Clinical Pharmacotherapy*, 4, 157 – 165.

Perkins, K., Jacobs, L., Sanders, M., & Caggiula, A. (2002). Sex differences in the subjective and reinforcing effects of cigarette nicotine dose. *Psychopharmacology*, 163(2), 194-201.

Prescott, E., Hippe, M., Schnohr, P., Hein, H., Vestbo, J. (1998) Smoking and risk of myocardial infarction in women and men: longitudinal population study. *Brit Med J* 316: 1043-1047.

Rose, JE. (2006) Nicotine and nonnicotine factors in cigarette addiction. *Psychopharmacology* 184: 274–285

Schneider N, Cortner C, Justice, M, et al. (2008). Preferences among five nicotine treatments based on information versus sampling. *Nicotine & Tobacco Research* 10: 179-186.

Schneider, N., Olmstead, R., Franzon, M., Lunell, E. (2001). The nicotine inhaler: Clinical pharmacokinetics and comparison with other nicotine treatments. *Clinical Pharmacokinetics*, 40, 661-684.

Shiffman S, Ferguson SG, Gitchell JG, Sembower MA, West R. (2009). Unplanned quit attempts--results from a U.S. sample of smokers and ex-smokers. *Nicotine & Tobacco Research*. 11(7):827-32.

Schiffman, S., Zervakis, J., Suggs, M., Cole-Budd, K. & Luga, L. (2000). Effect of tricyclic antidepressants on taste responses in humans and gerbils. *Pharmacology Biochemistry and Behavior*, 65, 599-609.

Schiffman, S., Zervakis, J., Suggs, M., Shaio, E. & Suttely, E. (1999). Effect of medications on taste: Example of Amitriptyline HCL. *Physiology & Behavior*, 66. 183-191.

Tepper, B., Christensen, C., Cao, J. (2001). Development of brief methods to classify individuals by PROP taster status. *Physiology & Behavior*, 73. 571-577.

USDHHS (1989) Surgeon General's Report: Reducing the health consequences of smoking.

West, R., Hajek, P., Foulds, J., Nilsson, F., Burrows, S., Meadows, A. (2000). A comparison of abuse liability and dependence potential of nicotine patch, gum, spray and inhaler. *Psychopharmacology*; 149:198-202.

West, R., Hajek, P., Nilsson, F., Foulds, J., May, S., Meadows A. (2001). Individual differences in preferences for and responses to four nicotine replacement products. *Psychopharmacology*; 153:225-230.

Zervakis, J., Graham, B. & Schiffman, S. (2000). Taste effects of lingual application of cardiovascular medications. *Physiology & Behavior*, 68, 405-413.

Zhao L, Kirkmeyer SV & Tepper BJ. (2003). A paper-screening test to assess genetic taste sensitivity to 6-n-propylthiouracil. *Physiology & Behavior*, 78, 625-633.

Westman, E., Behm, F., Rose, J. (1995). Airway sensory replacement combined with nicotine replacement for smoking cessation. : A randomized, placebo controlled trial using a citric acid inhaler. *Chest*, 107. 1358 – 1364.